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REVIEW

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Improvement of the therapeutic management of allergic patients in Europe – An expert think tank's position paper on allergen immunotherapy

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ABSTRACT

Respiratory allergies are a major global health issue due to their high prevalence and burden on patients, societies, and the health care system. In addition to symptom-relieving pharmacotherapy, allergen immunotherapy (AIT) is the only disease-modifying treatment option currently available that has the potential to prevent disease progression and the onset of asthma. The importance of AIT varies greatly from country to country. To discuss the different aspects of AIT, 20 experts from 12 European countries met for the First European Think Tank on Allergen Immunotherapy. The aim of the meeting was to formulate an expert position for improving the clinical care of patients with respiratory allergies in Europe, particularly concerning the use of AIT. The lacking class effect requires a product-specific assessment of AIT products for the most common allergens available in different European countries. Adherence, appropriate prescription, and early initiation – potentially to prevent disease progression – were identified as most important challenges for practical use of AIT. The shared decision-making on either sublingual or subcutaneous AIT may be based on safety and efficacy profiles, patient preferences, and clinical setting. Future challenges with regard to the application of AIT are as follows: to increase awareness for AIT among payers, health care providers, pharmacists, and patients; to better define patients who benefit the most of AIT; to improve the training of general practitioners on AIT as the first point of contact for allergy patients regarding allergy diagnosis and treatment, including AIT; to increase the awareness of AIT as a causal treatment option; to improve the training of primary care pediatricians with regard to AIT to ensure early initiation of AIT in cooperation with allergy specialists; to enhance the guidance of physicians through relevant AIT guidelines; and to provide them with more detailed scientific guidance for selecting the adequate products to achieve optimal benefits for their patients.

Keywords: Allergic rhinoconjunctivitis, Allergen immunotherapy, Unmet needs, Subcutaneous immunotherapy, Sublingual immunotherapy

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INTRODUCTION

More than 20% of the global population is suffering from respiratory allergic diseases which causes a high burden on societies and healthcare systems worldwide.[1]

While respiratory allergic diseases as allergic rhinitis and allergic asthma can be managed by symptom-relieving pharmacotherapy, allergen immunotherapy (AIT) is the only disease-modifying treatment of respiratory seasonal and perennial allergies that provides long-term clinical benefits.[2–4]

AIT's place in therapy is different across the different European countries. Although a beneficial impact of AIT in allergy therapy is recognized by allergic rhinitis guidelines, as in ARIA,[5] and recommendations on asthma, as in the GINA-report,[6] the importance of AIT in allergy treatment is considered relevantly different across the different European countries. Since the burden of the allergic disease is expected to increase with the progression of climate change[7] among other reasons, the adequate use of AIT is getting more and more relevant.[2–4]

Longitudinal studies show that school-aged children who are affected by pollen-induced allergic rhinitis are at high risk to develop a persistent allergic disease that continues also into adulthood; thus, there is a need for early interventions.[8]

Biomarkers to reliably monitor efficacy and response to AIT are still lacking, whereas knowledge about its immunologic mechanisms has greatly increased in the last few years.[9,10]

The following review outlines different aspects of AIT that were thoroughly discussed by the participants of the first European Think Tank on Allergen Immunotherapy (TTAIT) with the aim to formulate an expert position for improving clinical care of patients with respiratory allergies in Europe. To find a common understanding on the appropriateness of AIT's place in therapy for the treatment of allergic diseases and to discuss current challenges and opportunities, 20 allergy experts from 12 European countries (Belgium, Czechia, Denmark, Finland, France, Germany, Italy, The Netherlands, Norway, Poland, Spain, and Sweden) met for TTAIT, held in the Danish Embassy in Berlin, Germany on November 11, 2023. The meeting was supported by ALK, Germany. It was moderated by a professional moderator using the Metaplan technique. The aim of the meeting was to collect and critically discuss the different perspectives on the unity and variety of the European AIT landscape. Prior to the meeting, the specific circumstances in the different countries for the use of AIT were captured by face-to-face interviews with 1 member of each country represented in the meeting.

The first part of the review focuses on country-specific differences in Europe, ie, on availability of products, reimbursement, and applicability of AIT in general. Hereafter, common barriers for AIT in all European countries – ie, the importance of early initiation, adherence and treatment persistence, the urgent need for better training of prescribing physicians, and optimized product evaluation and selection based on solid evidence – are highlighted.

The consented key theses of this expert-meeting and Think Tank on Allergen Immunotherapy (TTAIT)-discussion including the current situation, barriers, unmet needs, and facilitators are highlighted in Table 1 and visualized in Fig. 1.

COUNTRY-SPECIFIC DIFFERENCES IN AIT APPLICABILITY AND ROUTINE USE

AIT products on the national level: how to tackle heterogeneity?

The experts agreed that, depending on the respective country, a large range of different products may be available eg, product-specific online information exists from Germany (tables provided by (i) the German allergy societies: https://dgaki.de/leitlinien/s2k-leitlinie-ait and[11] (ii) the German Federal Institute for Vaccines and Biomedicines (Paul-Ehrlich-Institut: https://www.pei.de/EN/medicinal-products/allergens/allergens-node.html).[12] No drug class effect (drugs seen as similar in their clinical effects and, therefore, considered interchangeable[13]) can be claimed for AIT products due to differences in the allergen source material, manufacturing processes, and standardization procedures used by the different manufacturers.[14] Therefore, efficacy

and safety should be evaluated as product-specific characteristics for the most common allergens (eg, house dust mites (HDM)/grass/birch and trees/ragweed) based on high quality clinical trials according to the requirements of the national competent authorities and the European Medicines Agency (EMA),[15] as stated in the "*Guideline on the clinical development of products for specific immunotherapy for the treatment of allergic diseases*".[16]

At the same time, it was agreed that, for rare allergens, it is not feasible to perform large clinical development programs. Data for long-term efficacy and cost effectiveness have not been investigated for most products available for

AIT	*Current situation*	Barriers	*Unmet needs and facilitators*
AIT products (SLIT and SCIT)	*Availability heterogeneous across Europe*	No class effect, regional & socioeconomic inequality	Product-specific evaluation of efficacy & safety
Age	*Limited data for patients >60 years, <5 years of age*	Inclusion of seniors & younger children in clinical trials problematic	Adequate trial designs
Poly-Allergy	*Treatment by AIT difficult*	No combination products (non-homologous allergen mixtures obsolete)	Treatment by 2 or 3 single allergen products with appropriate intervals between administrations
Start	*Often too late in the course of allergic disease*	Access to early diagnosis & treatment	Increased awareness of benefits & training of physicians
Adherence/ Persistence	*Suboptimal*	Patient education on treatment goals & side effects	Improve patient education, support patients by IT-solutions (eg, smartphone apps)
Biomarkers	*Not available for efficacy & response in routine use*	Complex immunologic mechanism of AIT	Data from further studies needed
AIT + biologics	*Data from studies on combined therapy limited*	High costs of biologics	More data on benefits of combined treatment with AIT + biologics needed
Evidence	*No clear criteria for evidence of efficacy & safety in the practice setting*	Evaluation of efficacy & safety difficult for practicing physicians	Definition of key criteria for physicians' evaluation of data from DBPC-trials
Reimbursement	*Varies widely in Europe*	Assessment of cost-/ benefit relation	All authorized products should be reimbursed
Training	*For prescribing physicians not optimal*	Low awareness & experience with AIT in primary care	AIT training of GPs; involving pediatricians to assure early treatment
General perception	*Recognition of benefits of AIT varies across European countries*	Low awareness of benefits of AIT for allergy treatment	Increased awareness by decision-makers (payers), health care providers, pharmacists, people with allergy

Table 1. AIT: Current situation, barriers, unmet needs and facilitators.

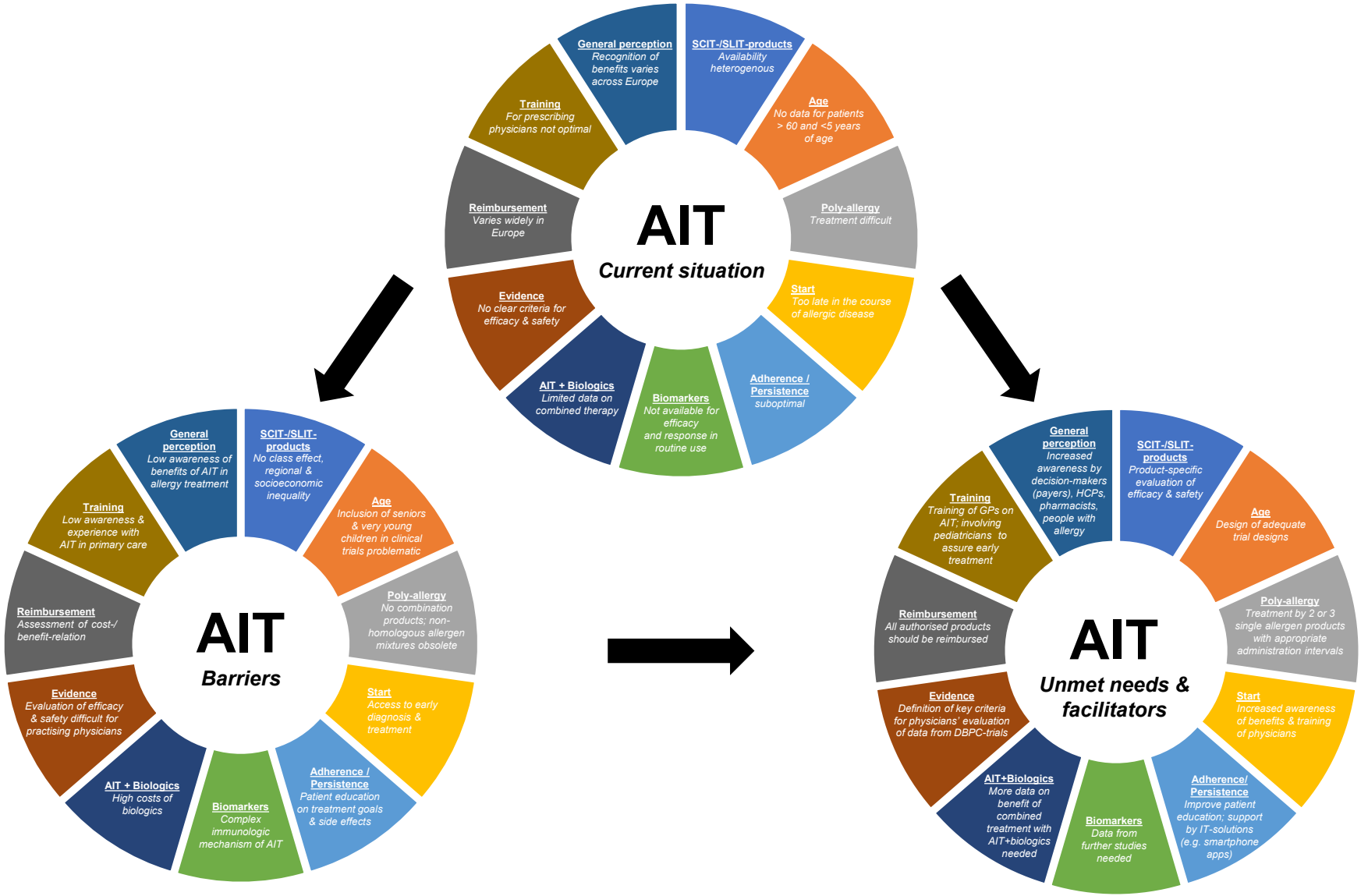

Fig. 1 AIT: Current situation – barriers, unmet needs & facilitators (visualizing Table 1).

prescription. Most patients with AR are poly-sensitized but clinically either mono-allergic (only homologous, biologically related allergens are driving symptoms) or poly-allergic (symptoms driven by overlapping exposure to multiple not homologous allergens).[2] True poly-allergic patients may be identified by molecular allergy diagnosis, also known as component-resolved diagnostics (CRD) by which the IgE-reactivity profile of patients at the molecular level is established. CRD may be helpful to identify true poly-allergic patients.[17] For poly-allergic patients who develop symptoms to allergens that are not homologous, the use of separate AIT preparations of the clinically most important allergens are recommended.[2] The experts had no common opinion on how to treat poly-allergic patients. However, there was a consensus that mixtures of non-homologous, biologically unrelated allergens should not be used anymore.[2,17,18] as recommended by EMA guidelines on production and quality issues of AIT products because of potentially lowered dose and allergen degradation owing to enzymatic activities of some allergens that may influence efficacy.[19]

Do marketing authorization and reimbursement influence the decision-making and the choice of AIT products?

Reimbursement for AIT products varies significantly across the different European countries. According to the experts, it would be desirable to achieve reimbursement for all products with a marketing authorization. While the marketing authorization is granted by the regulatory authorities based on data from clinical trials, the decision on reimbursement is mostly taken by other institutions (Health Technology Assessment (HTA) agencies) according to cost-effectiveness evaluations. Marketing authorization and reimbursement, however, are interconnected in countries where marketing authorization is a prerequisite for reimbursement. The experts agreed that reimbursement is an important criterion for the physician's and patient's shared decision on selecting a certain AIT product.

SCIT versus SLIT: how to find optimal solutions for individualized treatment?

The preference for AIT administered *via* the subcutaneous (SCIT) or sublingual route (SLIT) is heterogeneous within Europe and may be influenced by patients' and doctors' preferences, including individual factors (resources, living arrangements, work activity, place of residences, distance to the treating physician's office, etc.). While SCIT may be preferred by physicians in hospitals, which are better suited to treat possible severe adverse events, SLIT may be preferred in the physician's office due to easier and safer administration, fewer side effects and considering that less resources are needed. However, the adherence with SLIT at the beginning of therapy may be lower than with SCIT[20–22] requiring significant resources to monitor adherence. However, 3-year adherence seems to be similar between both application routes.[20] It was agreed that it is of highest importance to involve the patients and their preferences in the decision for SCIT or SLIT to increase adherence (shared decision-making).[23,24] Therefore, both treatment options should be presented to the patient. In France, SLIT is the only available route of administration except for insect venom immunotherapy. In Italy and Finland for example, SLIT is also preferred in hospital settings (ie, tertiary health care) due to resource limitations, such as staff shortage. From a perspective on environmental protection, SLIT is able to reduce commuting and travelling of patients and related costs and may, thus, be, more environmentally sustainable.[25–28]

Biologics fostering efficacy of AIT: is combination therapy the future?

AIT has been the first truly personalized medicinal treatment based on the patient's immunological profile.[29] More research is needed in the use of AIT in combination with other allergy treatments, in particular biologics that are becoming increasingly investigated and used,[17] although connected with exceptionally high costs.

In several clinical studies a combination of AIT, mainly SCIT, with monoclonal antibodies like anti-IgE (omalizumab), anti-IL-4 (VAK694), anti-IL-4/IL-13Rα (dupilumab), and anti-thymic stromal lymphopoietin (TSLP) was investigated.[17] Combining SCIT with omalizumab in patients with allergic rhinitis increased tolerability and, in combination with ragweed AIT, efficacy. In patients with HDM-related asthma, the efficacy of the combination

therapy was increased versus the single therapies.[17]

Hypothetically, a combination therapy with AIT and biologics may enhance the long-term efficacy on rhinitis and asthma symptoms, and the improvement of lung function, and potentially change the natural course of severe asthma and increase remission.[30]

Suboptimal recognition of AIT's benefits: how to overcome country-specific differences?

The experts agreed that awareness of AIT and its benefits on allergic rhinitis and asthma should be improved not only among decision-makers (payers), but also health care providers, pharmacists, and affected individuals with allergies. The level of specialization and training in allergy treatment is very heterogeneous across Europe. While the number of allergy specialists is high in some countries (eg, Poland), the number of specialists is very low in other countries (eg, Belgium).[31] The general perception of AIT was impaired for a long time, and partly still is. Lack of knowledge, allergen products of poor quality due to highly diluted extracts and/or inappropriate prescriptions for patients often lead to disappointing outcomes.

In summary, AIT is the only allergy treatment with disease-modifying and preventive potential. The awareness of AIT should be raised among decision-makers, health care providers, pharmacists, and individuals with allergies. A large range of AIT products, with and without marketing authorization (MA), is available in the different European countries. It is necessary to differentiate between named patient products (NPPs) and products with MA: products with MA have been assessed by a competent authority for their quality, efficacy and safety in concordance with EMA guidelines (eg, Guideline on clinical development of AIT products);[16] in contrast, this is not the case for NPPs. The treating physicians should be encouraged to gain insights into the MA status of all products they use, particularly because there is no class effect. Due to the safety profile, SCIT may be preferred by physicians in hospitals and SLIT by physicians in the office. Promising results from studies with combination of biologics and AIT were reported. The increasing evidence from clinical trials may help to increase acceptance as well as reimbursement of AIT products, which currently varies significantly among different European countries.

COMMON BARRIERS FOR AIT IN ALL EUROPEAN COUNTRIES

Initiation of AIT in an early stage of the disease: why is it so important?

A prerequisite that is crucial for the success of AIT, according to the experts, is to identify the right patient by establishing the adequate diagnosis. In many cases, the patient is on an odyssey for many years before being appropriately diagnosed and adequately treated.

AIT should be initiated as early as possible.[2,14] AIT is usually first considered when the patient's allergy has emerged as allergic rhinitis, while in clinical trials patients are included with allergic rhinitis being insufficiently controlled by symptomatic treatment. Very little data is available on young children below 5 years of age and on the best time for initiation of AIT in young children. The GRAZAX Asthma Prevention trial (GAP) has shown that the number-needed-to-treat to prevent 1 additional child from having asthma symptoms and needing asthma medication increased with age indicating that earlier treatment may be even more effective.[32,33] More data for specific patient groups such as senior patients above 60 years and children below 5 years of age are needed. The patients that may benefit the most from AIT should be better defined and respective guidance provided by AIT guidelines. Early diagnosis and treatment should be ensured on a more systematic level to avoid that patients do not receive the adequate diagnosis and subsequent treatment.[34]

Adherence to AIT: how can it be improved?

As for other chronic diseases, retrospective studies from prescription databases, have demonstrated that adherence and persistence is suboptimal in AIT.[20,21,35,36] The experts agreed that treatment with SCIT and SLIT should ideally be monitored with regular follow-up visits. Adherence to AIT may be improved by providing IT-tools as smartphone apps (eg, MASK-air:

https://www.mask-air.com [37] or GALENUS HEALTH: https://www.galenus.health/ [38])[39] allowing patients to record their symptoms, use of symptomatic medication and patient reported outcomes (PROs) on quality of life to monitor their benefits of treatment according to standardization of outcomes in allergic rhinitis and asthma as published in European Academy of Allergy and Clinical Immunology (EAACI) position papers.[40,41] In an observational study in Italy, the adherence to daily recording in an e-diary was very high when prescribed and motivated by an allergist in a blended care setting.[42]

Training of prescribing physicians: why is this so important and how to optimize?

To be able to treat allergic patients, training on AIT should be improved at the basic health care level. In a cross-sectional, observational study a structured electronic questionnaire was distributed to primary care providers in 8 European countries; less than half of the respondents had received some undergraduate and/or post-graduate allergy education, and 1 in 5 had not received any training on allergic diseases. The majority of respondents expressed a great lack of confidence in identifying patients who needed a referral to a specialist, particularly for AIT.[43]

By patient-centered communication among health care providers an effective integrated model of care for patients with allergic diseases can be provided.[44]

Few training facilities with a strong focus on AIT are available across Europe. As published in an EAACI position paper, a substantial heterogeneity was reported regarding recognition of allergology as a full specialty, the number of practicing specialists or subspecialists, and training aspects.[31] The approach to AIT should be shared already during specialization in the various specialties. The minimal requirements for training and certification of subspecialists in allergology were proposed by the EAACI specialty committee.[45]

It was discussed controversially which level of training and specialization of physicians would be needed for them to properly prescribe AIT. This is discussed in the context of the high prevalence of respiratory allergies, the predicted increase in their incidence, and a high number of patients that will require this treatment. Ideally, from a patient's/caregiver's perspective, candidates for AIT should be identified and treated by the physician they initially present to in cooperation with specialists.[46] It is important that the physician is suitably trained and experienced. A stronger focus on patients is highly needed to properly manage allergic diseases in general, including the use of AIT. According to the Summary of Product Characteristics (SmPC) of most products, AIT should be initiated by physicians experienced in treating allergic diseases. General practitioners (GPs) may often be the first physicians consulted by allergic patients. Besides, pediatricians should be preferably involved in AIT treatment, as AIT is the ideal treatment for type 1 allergies in children due to its potential preventive effects. Early involvement of a higher number of pediatricians in Europe would allow more children and adolescents to benefit from earlier treatment. To summarize, an improved training of health care professionals involved in the treatment of allergic patients comprising specialists, but also GPs and pediatricians is an important unmet need.

How to select the best product?

The EAACI guidelines on AIT[2,47] state that products with documented evidence of efficacy and safety should be preferably used. However, the experts agreed that clear criteria for the requested evidence for efficacy and safety are missing in the practical setting. Therefore, physicians should be provided with more guidance to select the right product for the right patient. This depends on the availability of products with marketing authorization or named patient products (NPPs), and the documentation of efficacy and safety.

Products with marketing authorization based on state-of-the-art double-blind, placebo controlled (DBPC) -clinical trials in line with the prerequisites of the national and European competent authorities should preferably be used. Products with these characteristics should be regarded as efficacious with an acceptable safety profile and used as first choice. As second-line options, products without marketing authorization, but with

evidence for efficacy and safety from DBPC-clinical trials are recommended.

Physicians may assess a specific product by verifying the following key criteria with respect to available data from DBPC-clinical trials: As evidence for efficacy, only predefined criteria should be taken into consideration (primary and secondary endpoints), i.e., endpoints included as part of the experimental design in public databases (*European Union Clinical Trials Register/Clinical Trial Information System;* https://www.clinicaltrialsregister.eu/; https://euclinicaltrials.eu/) or the *U.S. Department of Health and Human Services*; https://clinicaltrials.gov). As primary endpoint, a combined symptom and medication score (CSMS) versus placebo is frequently chosen. Trials should be checked for adequate statistical power, analysis according to intention-to-treat (IIT) or full analysis set (FAS), (Table 2). Post-hoc analyses may be regarded as supporting information but cannot replace the outcomes of predefined criteria.

The experts suggested that independent organizations of health care professionals like EAACI may update existing AIT guidelines and evaluate the available data for all products from the most common allergen sources (grass, birch, HDM) and national allergy societies and may complement data on the clinical documentation of products from allergen sources that are locally relevant (eg, olive and *parietaria* for the Mediterranean countries).

Key criteria for state-of-the-art clinical trials in AIT:
• Significant and clinically relevant difference vs. placebo with combined symptom and medication score as primary endpoint:
• Predefined primary and secondary endpoints (post-hoc analysis only as supportive information)
• Adequate statistical power
• Analysis according to intention-to-treat (ITT) or full analysis set (FAS)
• Marketing authorization granted based on trial results

Table 2. AIT: Key criteria for state-of-the-art clinical trials.

CONCLUSION

In conclusion, the right patient for AIT must be identified by adequate diagnosis as early as possible. More data on AIT in specific age groups, such as seniors >60 years and younger children <5 years are needed. Patients who will benefit the most from AIT should be better defined, and the corresponding guidance provided by the AIT guidelines. To improve adherence and persistence of AIT, patients should ideally be monitored with regular follow-up visits and be provided with adequate IT-tools like smartphone apps. The AIT-training for physicians who are initially consulted by patients - mainly GPs - should be improved and pediatricians should be involved to ensure early treatment and benefit from preventive effects of AIT. To give the right product to the right patient, more scientific guidance is needed on how to evaluate evidence from DBPC-trials according to key criteria. Products with a marketing authorization should preferably be used. Independent organisations of health care professionals like EAACI may evaluate available data for products from grass, trees, and HDM as the most common allergen sources, and national authorities may complement data from locally relevant allergen sources.

Taken together, participants in the first European TTAIT underscored that AIT, as an immunomodulatory treatment option, is an important therapeutic pillar for patients with allergic diseases. Evidence from state-of-the-art clinical trials with specific products is increasing, particularly in the pediatric population. Currently, products with marketing authorization and NPPs are available according to different regulatory requirements across Europe. As challenges for the practical use of AIT, adherence, appropriateness of prescription (the right product to the right patient), and early initiation to benefit from the preventive effects of AIT were identified. To achieve these goals, the experts agreed that the level of allergy training for primary care physicians, including pediatricians, should be improved and that more detailed scientific guidance for selecting adequate products to achieve the highest possible benefits from AIT for each individual patient is needed (see Table 1, Fig. 1).

Abbreviations

AIT: Allergen immunotherapy; CRD: Component-resolved diagnostics; CSMS: Combined symptom and medication score; DBPC: Double-blind, placebo-controlled; EMA: European Medicines Agency; FAS: Full analysis set; GAP: GRAZAX Asthma Prevention trial; GP: General practitioner; HCP: Health care provider; HDM: House dust mite; HTA: Health Technology Assessment; ITT: Intention to treat; MA: Marketing authorization; NPP: Named patient product; PROs: Patient reported outcomes; SCIT: Subcutaneous immunotherapy; SLIT: Sublingual immunotherapy; SmPC: Summary of Product Characteristics; TTAIT: Think Tank on Allergen Immunotherapy.

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Not applicable, as this is a review paper.

Declaration of competing interest

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All authors agree to the publication of this work.

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